

AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 07: Diabetes Mellitus

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www.ahrq.gov

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Prepared by:

ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the National Academy of Medicine (formerly the Institute of Medicine) and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

Richard Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

David Meyers, M.D.
Acting Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 21,000 leads about potential topics has resulted in identification and tracking of about 2,250 topics across the 14 AHRQ priority areas and 1 cross-cutting area; more than 600 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 170 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

Results

The table below lists the five topics for which (1) preliminary phase III data for drugs, at least phase II or equivalent data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled before May 8, 2015, in this priority area; *and* (3) we received five to seven sets of comments from experts between July 1, 2014, and May 18, 2015. (Seventeen topics in this priority area were being tracked in the system as of May 8, 2015.) All five topics (indicated below by an asterisk) emerged as having high-impact potential on the basis of experts’ comments and assessment of potential impact, and we present summaries below. The material on interventions in this Executive Summary and report is organized alphabetically by disease state and then by intervention. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 07: Diabetes

Topic	High-Impact Potential
1. * Extended-release exenatide delivered by implanted osmotic pump (ITCA 650) for treatment of type 2 diabetes	Lower end of the high-impact-potential range
2. * Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema	Lower end of the high-impact-potential range
3. * Metabolic surgery for treatment of type 2 diabetes mellitus regardless of patient BMI	High
4. * Threshold-suspend/Low-glucose-suspend Insulin Delivery Systems for Managing Hypoglycemia in Patients with Type 1 Diabetes Mellitus	High
5. * Ultra-rapid acting inhaled insulin (Technosphere insulin inhalation system with Afrezza) for treating diabetes that requires insulin	Lower end of the high-impact-potential range

Discussion

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia (elevated blood sugar). Diabetes-associated hyperglycemia results from dysfunction in either insulin secretion or insulin action or both. Most diabetes mellitus cases are either type 1 diabetes mellitus (T1DM; 5% of cases) or type 2 diabetes mellitus (T2DM; about 95% of cases). The American Diabetes Association (ADA) reports that about 29.1 million children and adults in the United States have diabetes mellitus, but only about 21 million have received a formal diagnosis. Furthermore, about

86 million people in the United States have prediabetes or are at risk of developing T2DM. ADA stated that clinicians diagnosed 1.7 million new cases of diabetes in U.S. people aged 20 years or older in 2012 (the most recent year for which statistics are available).

T1DM risk factors include family history of T1DM and presence of certain genetics, whereas T2DM risk factors include being overweight, having a body that primarily stores fat in the abdomen, having a family history of the disease, or having another form of diabetes mellitus such as prediabetes or gestational diabetes. Being African American, Hispanic, American Indian, or Asian American is also a risk factor for T2DM. According to the U.S. Centers for Disease Control and Prevention (CDC), diagnosed T2DM is seven times as prevalent in adults aged 65 years or older as in adults aged 20–44 years.

ADA states that T1DM is caused by destruction of pancreatic beta cells, preventing secretion of insulin, and that this destruction is either immune mediated or idiopathic, with immune-mediated destruction accounting for the majority of cases. T1DM can occur at any age, but is most often diagnosed in children, adolescents, or young adults. Patients with T1DM require insulin therapy.

In T2DM, hyperglycemia is a result of insulin resistance or a diminished response to insulin. ADA states that patients with T2DM also often have a relative insulin deficiency and may have an insulin secretory defect in conjunction with insulin resistance.

Clinicians use one of three tests to diagnose diabetes mellitus: fasting plasma glucose test, oral glucose tolerance test, and casual plasma glucose level measurement. A fasting plasma glucose level of 126 mg/dL or more, an oral glucose tolerance test reading of 200 mg/dL or more, or a casual plasma glucose level of 200 mg/dL or more in conjunction with hyperglycemia symptoms all signal a diabetes diagnosis.

Additionally, a glycated hemoglobin (HbA_{1c}) test may be performed. This test indicates the patient's average blood sugar level for the previous 2 or 3 months, and an HbA_{1c} level of 6.5% or higher on two separate tests is considered to be diagnostic of diabetes. HbA_{1c} levels ranging from 5.7% to 6.4% indicate a diagnosis of prediabetes, with normal levels below 5.7%.

Treating and managing diabetes to prevent complications require patients to make a lifelong commitment to exercising regularly, maintaining a healthy weight, eating healthy foods, monitoring blood sugar, and, in some cases, taking insulin. The primary treatment goal is to maintain blood sugar levels as close to normal as possible to delay or prevent complications.

After diagnosis and disease-type classification, patients undergo evaluation to detect complications, review glycemic control challenges, and establish treatment goals and a treatment plan. Clinicians generally encourage patients to achieve an HbA_{1c} level of 7% or lower because this value has been shown to reduce diabetes-associated microvascular complications. However, targets are individualized according to clinician judgment about the optimal goal for a specific patient.

For T2DM, several self-administered, oral antidiabetes agents, alone or in combination, are generally tried as first-line therapy. These include biguanides, sulfonylureas, alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, and dipeptidyl peptidase-4 inhibitors. Many patients with T2DM do not meet treatment goals and require additional therapy with one of two types of injected antidiabetes agents: subcutaneous insulin or a glucagon-like peptide-1 (GLP-1) agonist. Insulin supplementation has become increasingly common with T2DM.

Most new treatments in development for diabetes focus on delaying disease onset in at-risk patients, improving diabetes management and treatment adherence, and for T1DM, developing options that prevent the body's autoimmune reaction against pancreatic islet cells or mimic the natural function of the pancreas to produce insulin. Some emerging technologies, such as the Iluvien implant, target treatment of serious complications of diabetes, such as diabetic macular edema (DME). The American Academy of Ophthalmology (AAO) defines DME as swelling or thickening of the macula, a thin layer of light-sensitive tissue that lines the back of the eye and is

responsible for detailed central vision. Macular edema develops when blood vessels in the retina leak, causing the macula to swell and impairing its function. AAO states that DME is the most common form of vision loss for people with diabetes, particularly if left untreated.

Eligible Topics Deemed High Impact

Diabetes Mellitus

Extended-Release Exenatide Delivered by Implanted Osmotic Pump (ITCA 650) for Treatment of Type 2 Diabetes

- **Key Facts:** ITCA 650 is extended-release exenatide for injection (Bydureon™), delivered through a proprietary system consisting of a “matchstick-sized osmotic pump” that is inserted subcutaneously to deliver a slow and consistent flow of exenatide. Exenatide, a GLP-1 receptor agonist that has been available since 2005, is an incretin mimetic that patients inject twice daily, before meals. The ICTA 650 implant is intended to be used for long-term subcutaneous delivery at a controlled rate for treating T2DM. ITCA 650 is reported to remain stable at body temperature for delivery up to 12 months, based on data presented thus far. The outpatient implantation procedure is performed by a physician and takes about 10 minutes.

In June 2015, the company announced study results from the phase III FREEDOM-1 and FREEDOM-1 High Baseline (HBL) trials in a press release. According to ITCA 650’s manufacturer, FREEDOM-1 met all key endpoints. ITCA 650 produced mean reductions in HbA_{1c} of 1.4% at 39 weeks of treatment. Weight loss over 39 weeks depended on drug dose, with patients who received 60 mcg/day losing a mean of 4 kg at 39 weeks, compared with a 2 kg weight loss in the placebo group. Investigators observed no new safety concerns for the implant. The company also reported that 60 patients in FREEDOM-1 HBL had a 3.4% mean reduction in HbA_{1c}, with 22% of patients achieving HbA_{1c} reductions of 4% or greater at 39 weeks. (We believe the results for HbA_{1c} that the company stated as percent changes should instead be expressed as percentage points.) The manufacturer expects to file for regulatory approval of ITCA 650 to the U.S. Food and Drug Administration (FDA) in 2016. No information is available about anticipated costs.

- **Key Expert Comments:** Experts generally agreed on the need for effective T2DM treatments, citing patient adherence issues and the lack of consistent efficacy of available treatments. They agreed on the potential of this intervention to reduce the burden of frequent injections and to provide consistent, effective treatment. Most experts opined that both clinicians and patients would be likely to accept this intervention. One expert anticipated wide physician adoption if the procedure is reimbursed separately to become a new revenue stream. Most experts predicted that the initial cost of the device would likely be offset by the long-term savings from reduced disease-related complications, if proved effective.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Metabolic Surgery for Treatment of Type 2 Diabetes Mellitus Regardless of Patient BMI

- **Key Facts:** Metabolic surgery for T2DM has evolved as an intervention intended to induce remission in patients who have been unable to achieve adequate blood glucose control with first- and second-line therapy. Investigators have observed that bariatric surgery to reduce body weight in obese patients also offered an additional benefit of restoring metabolic

imbalances and promoting diabetes remission in many patients. Metabolic surgeries for T2DM have been typically classified as purely restrictive, restrictive/malabsorptive, or purely malabsorptive. Restrictive procedures limit food consumption, while malabsorptive procedures reduce food absorption. Researchers hypothesize that the effect of metabolic surgeries extend beyond those of malabsorptive and restrictive strategies. Although the exact mechanisms of diabetes remission are unclear, researchers believe they are associated with multiple changes to patient anatomy and physiology, resulting in metabolic alterations.

- **Key Expert Comments:** Most experts cited a growing population with T2DM that is often inadequately managed as demonstrating a large unmet need. Several experts noted metabolic surgery's potential to put T2DM into remission rather than just manage the condition as supporting its large potential to improve patient health and fill a large unmet need. According to most experts, metabolic surgery represents a substantial disruption to how most patients with T2DM are managed, compared with more conservative options such as pharmacotherapy and diet and lifestyle modification. Overall, experts expected that established bariatric surgery programs could add metabolic surgery to their programs with minimal disruption, unless insurance coverage becomes widely available and substantial patient demand develops.
- **High-Impact Potential:** High

Threshold-suspend/Low-glucose-suspend Insulin Delivery Systems for Managing Hypoglycemia in Patients with Type 1 Diabetes Mellitus

- **Key Facts:** The MiniMed 530G with Enlite[®] sensor is an external insulin pump used in combination with a continuous glucose monitoring sensor that can stop insulin delivery when a patient's blood glucose reaches a prespecified low level. FDA approved the MiniMed 530G system in September 2013 as the first insulin pump available in the United States to incorporate a low-glucose suspend (LGS) algorithm feature; the LGS algorithm automatically stops insulin delivery for up to 2 hours when sensor glucose values reach a preset level and the patient does not respond to the threshold-suspend alarm. The indication is "for use by people with diabetes ages 16 and older, requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin." This system is the first to be approved under FDA's new product classification, "OZO: Artificial Pancreas Device System, Threshold Suspend." It is especially intended for use in patients who experience hypoglycemia without being aware of it. The system consists of components that can be used in combination or individually: insulin pump capable delivering insulin and storing 90 days of pump history and glucose sensor data; Enlite sensors for continuous glucose monitoring (disposable, can be worn for six days); Enlite Serter that aids sensor insertion; MiniLink Real-Time transmitter that, when connected to a sensor, automatically initializes the sensor and periodically sends glucose data to the pump using a radio signal; Bayer Contour NextLink glucose meter that transmits fingerstick blood glucose results wirelessly to the insulin pump; Bolus Wizard, which suggests a bolus amount to users based on their personal settings, blood glucose readings, carbohydrate entry, and active insulin levels; CareLink Pro Therapy management software that uses information transmitted from insulin pumps, glucose meters, and CGMs to generate reports that can be used to identify trends and track daily activities (e.g., carbohydrates consumed, meal times, insulin delivery, glucose readings); CareLink Personal Therapy management software that uses information transmitted from insulin pumps, CGMs, and glucose meters, and logbook data entered by the patient to generate personal reports.

Users insert the glucose sensor through the skin in the abdomen to measure glucose values in the interstitial tissue. These values are transmitted to and displayed on the insulin

pump. The insulin pump delivers a small preset basal dose of rapid-acting insulin to the patient through an infusion set (a flexible delivery cannula with a small needle on the end) inserted under the skin in the abdomen. Users must change the infusion site every two to three days. Also, users must perform a minimum of four fingerstick blood glucose tests per day using a glucose meter and manually administer individualized bolus doses of rapid-acting insulin via the pump to cover food intake and correct for high glucose levels. The system requires a prescription.

Estimates list the retail price at \$7,350, with insured patients reporting copayments from \$5 to up to 50% of costs. Medtronic introduced the Path2System Program to aid adoption by existing insulin infusion pump users. According to the company, patients using the Paradigm® Revel™ Insulin Pump and Continuous Glucose Monitoring (CGM) system with a valid warranty can obtain the new MiniMed 530G system for \$399 plus the varying cost of the Enlite starter kit. Patients' out-of-pocket costs for CGM vary according to their health plan coverage. The Path2System includes the MiniMed 530G insulin pump; Enlite training packet; MiniLink transmitter, charger and test plug; and Enlite Starter Kit. For patients currently using a Medtronic CGM, the estimated cost to obtain the MiniMed 530G System and use it for a year would be about \$7,975. The system requires frequent replacement of the Enlite sensors that cost about \$4,500 per year per patient. Many third-party payers cover the system according to its labeled indication for patients who meet criteria for an external insulin pump.

- **Key Expert Comments:** Overall, experts agreed on the need for systems that help patients achieve adequate glucose control. Most experts commenting on this intervention opined that it has the potential to improve patient health outcomes by reducing hypoglycemic episodes. Experts generally agreed that both patients and clinicians would adopt this intervention. However, some experts cited cost, insurance coverage, and device training to be potential barriers to acceptance. Most experts thought the technology would likely not affect health care disparities, but some thought the high cost and complexity could impede access for some populations.
- **High-Impact Potential:** High

Ultra-Rapid-Acting Inhaled Insulin (Technosphere Insulin Inhalation System With Afrezza) for Treating Diabetes That Requires Insulin

Key Facts: The Technosphere® insulin inhalation system with Afrezza® powdered insulin is a noninjectable, rapid-acting form of prandial (mealtime) insulin therapy intended to improve glycemic control in adult patients with T1DM or T2DM. In June 2014, FDA approved Afrezza for improving glycemic control in adults with diabetes mellitus. FDA required a Risk Evaluation and Mitigation Strategy (REMS) for Afrezza approval, informing prescribers about potential associated risks including the serious risk of acute bronchospasm. FDA recommends that Afrezza should not be used in patients with chronic lung disease, such as asthma or chronic obstructive pulmonary disease, because of this risk. In February 2015, the co-developers initiated a commercial rollout of prescription Afrezza to retail pharmacies throughout the United States. Inhaled insulin has not been compared to injected insulin in large randomized, controlled trials. Available data reported by the manufacturers suggest that Afrezza therapy was associated with reduced pulmonary function that occurred during the first 3 months of therapy and persisted over 2 years.

- **Key Expert Comments:** Experts anticipated that the growing population with diabetes increases the importance of new developments to improve patient adherence to

recommended therapy. Experts generally expected wide acceptance for inhaled insulin from prescribing physicians and patients. Some experts thought that higher costs than injectable insulin and availability of insurance coverage could affect access to this therapy for less-affluent patients. Experts anticipated minimum disruption overall to health care infrastructure and patient management. However, several experts noted that patients will need to be screened for pulmonary conditions to be eligible for inhaled insulin.

- **High-Impact Potential:** Lower end of the high-impact-potential range

Diabetic Macular Degeneration

Fluocinolone Acetonide Implant (Iluvien) for Treatment of Diabetic Macular Edema

- **Key Facts:** Laser photocoagulation to halt vision loss is the standard treatment for diabetic macular edema (DME), but this treatment cannot reverse vision loss that has already occurred and somewhat increases the risk of losing peripheral, night, or color vision. Injections of steroids or other agents may be used to treat DME but require repeated intravitreal injections to maintain therapeutic effect. Iluvien® is a tiny tube containing the steroid fluocinolone acetonide that is injected once into the back of the eye and releases the drug slowly over 3 years to provide a combined vasoconstrictive and anti-inflammatory, and effect. In September 2014, FDA approved Iluvien for treating DME in patients “who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.” Fluocinolone acetonide’s potential risk of increasing intraocular pressure might dissuade some physicians from embracing fluocinolone acetonide implants to treat DME until a larger body of evidence becomes available.
- **Key Expert Comments:** Overall, experts commenting on this intervention opined that this intervention could offer a long-lasting, single-procedure pharmacotherapy as an alternative to laser photocoagulation or repeated injections of ranibizumab (Lucentis®) or other agents for treating DME. Experts expressed concerns regarding potential adverse events, including cataracts and increased intraocular pressure. Experts generally agreed that this intervention has the potential to be accepted by patients and clinicians because it may offer benefit up to 3 years. However, several experts commented that the risk of adverse events could affect patient and clinician adoption. Several experts noted that the intervention has the potential to reduce per-patient costs of treatment. However, experts also cautioned that cost savings could be nullified if patients need to be treated for device-related adverse events, such as cataracts or glaucoma.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Diabetes Mellitus Interventions

Continuous Subcutaneous Delivery of Exenatide by Implantable Pump (ITCA 650) for Treatment of Type 2 Diabetes

Unmet need: Despite the availability of oral antidiabetes drugs, many patients with type 2 diabetes mellitus (T2DM) do not meet treatment goals and require additional therapy with one of two types of injected antidiabetic agents: subcutaneous insulin or a glucagon-like peptide 1 (GLP-1) receptor agonist, also called an incretin mimetic.¹ Incretin mimetics have become standard treatments to improve glycemic control.² However, the GLP-1 receptor agonists approved by the U.S. Food and Drug Administration (FDA)—exenatide (Byetta®), liraglutide (Victoza®), and exenatide extended release (Bydureon™)—require twice-daily, once-daily, or once-weekly dosing, respectively, by subcutaneous injection.^{3,4} More convenient dosing could potentially improve adherence to treatment recommendations and patient outcomes.

Intervention: ITCA 650 is a matchstick-sized, implantable device that is intended to deliver a steady dose of an incretin mimetic, exenatide, using a proprietary delivery system (Duros® technology) for up to 12 months.⁵ Exenatide, which has been available since 2005, is an incretin mimetic that patients inject twice daily, before meals. The new Duros delivery system is intended to deliver the drug subcutaneously, at a controlled rate over the long term. It has been used commercially since 2000 in a leuprolide acetate implant (Viadur®) for treating advanced prostate cancer.⁶

The system is a miniature osmotic pump that essentially functions as a syringe.⁶ Within a tubular titanium shell, the system contains a drug reservoir and an osmotic agent separated by a piston. Adjacent to the osmotic agent is a semipermeable membrane. The osmotic agent steadily draws water from the body across the membrane, which exerts pressure on the piston, forcing a steady flow of drug out of a small pore or diffusion moderator on the opposite side of the pump. Studies have demonstrated that the formulation of exenatide used in ITCA 650 is stable within the Duros pump for at least 1 year at body temperature, potentially allowing once-yearly system implantation.⁷

A physician inserts ITCA 650 under the skin during an outpatient procedure that takes about 5–10 minutes.^{8,9} Clinicians can remove or replace the device in a similarly short procedure. The version of ITCA 650 that will be used in phase III clinical trials is intended to deliver a dose of 60 mcg of exenatide per day.^{8,10}

Clinical trials: In March 2013, ITCA 650's developer announced enrolling the first patients in its phase III FREEDOM clinical program, which is expected to include more than 4,000 patients at 500 clinical trial sites in more than 30 countries. The studies will include a broad range of patients whose diabetes is uncontrolled by oral antidiabetes medications including metformin and metformin-based combinations.¹⁰

In June 2015 at the American Diabetes Association annual scientific sessions, the company announced study results from two phase III trials in the FREEDOM program (FREEDOM-1 and FREEDOM-1 High Baseline [HBL]) in a press release.¹¹ FREEDOM-1, a placebo-controlled study, demonstrated positive results for ITCA 650 when added to diet and exercise with or without standard oral diabetes medications, for those patients who were not at goal. According to the manufacturer, all key endpoints were met. ITCA 650 produced mean reductions in glycated hemoglobin (HbA_{1c}) of 1.4% at 39 weeks of treatment. Patients on a background regimen including a sulfonylurea drug (47% of patients) had a mean HbA_{1c} reduction of 1.2%. Patients on a non-sulfonylurea background regimen, including primarily metformin-based regimens (about 40% of patients), or diet-and-exercise regimens (about 11% of patients), showed a mean HbA_{1c} reduction of 1.7%. Weight loss over 39 weeks depended on drug dose. “Patients on the primary phase 3 dosing

regimen lost a mean of 4 kg in the 60 mcg/d ITCA 650 dose group vs. 2 kg in the placebo group at Week 39, which was statistically significant,” the company reported. Investigators observed no new safety concerns beyond what is known for the GLP-1 receptor agonist class. The company reported that tolerability was similar between the 40 mcg per day and the higher 60 mcg per day dose groups. According to the press release, “There was a low single-digit discontinuation rate for nausea. Other adverse events associated with the administration site and the procedures to place and remove the ITCA 650 were generally mild and transient. Discontinuations due to procedures and administration site adverse events were also a very low single digit rate across each arm of the 39-week study.”¹¹

The press release also reported on 60 patients in FREEDOM-1 HBL who had a 10.8% mean HbA_{1c} level, a mean 32.0 kg/m² body mass index, and mean 9-year diabetes duration at baseline. By 39 weeks, patients had a 3.4% mean reduction in HbA_{1c}, with 22% of patients achieving HbA_{1c} reductions of 4% or greater and 25% of patients achieving an HbA_{1c} level of less than 7% at the last observation carried forward endpoint. Investigators observed weight loss in patients that did not achieve statistical significance.¹¹

In May 2013, Henry and colleagues reported on the safety and efficacy of the ITCA 650 pump system compared with twice-daily exenatide injections (Ex-BID) from a two-stage, phase II trial in patients with T2DM inadequately controlled with metformin.¹² Stage I (n=155) evaluated patient outcomes after 12 weeks of treatment with 20 or 40 mcg/day of ITCA 650 or Ex-BID. Stage II (n=131) randomly reassigned patients to receive 20, 40, 60, or 80 mcg/day of ITCA 650 for an additional 12 weeks. They reported that HbA_{1c} was significantly lower in all study groups after 12 and 24 weeks. Stage I mean change in HbA_{1c} (from a mean baseline of 7.9% to 8.0%) for the 20 and 40 mcg/day ITCA 650 and Ex-BID groups was 0.98% lower, 0.95% lower, and 0.72% lower, respectively. HbA_{1c} levels of 7% or less were achieved by 63%, 65%, and 50% of patients, respectively (p<0.05). Stage II patients had significant (p<0.05) reductions in HbA_{1c} (about 1.4 percentage points from baseline) with 60 and 80 mcg/day ITCA 650; at 24 weeks, 86% and 78% of patients had HbA_{1c} of 7% or less; respectively. Weight reductions were also observed—a loss of 2.8 to 3.7 kg (p<0.05) at 24 weeks in all except the group that received 20 mcg/day in both stages of the trial. ITCA 650 was reported to be well tolerated.¹²

Manufacturer and regulatory status: Intarcia Therapeutics, Inc. (Hayward, CA), is developing the ITCA 650 system for continuous subcutaneous delivery of exenatide using extended-release exenatide for injection (Bydureon™), made by AstraZeneca (London, UK). In November 2014, Intarcia announced a partnership that grants exclusive rights to Servier (Neuilly sur Seine, France) to market the ITCA 650 system outside of the United States and Japan.¹³ The company anticipates submitting a premarket approval application to FDA in 2016.⁵

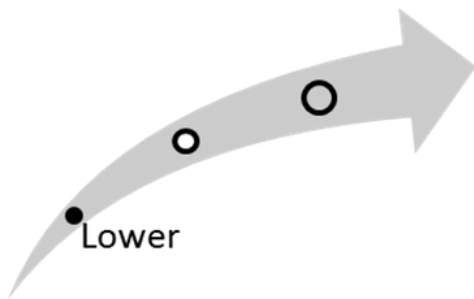
Diffusion: If it receives FDA approval, ITCA 650 is most likely to compete with injected exenatide extended release (administered once weekly) and liraglutide (administered once daily).^{3,4,14} The cost for ITCA 650 has not been determined, but it will likely be priced at a slight premium to existing injectable exenatide formulations because of its novelty and convenience.¹⁵ Although ITCA 650 use would add to the upfront cost of therapy, it could potentially save costs if it improves patient adherence to prescribed treatment, slows disease progression and development of secondary complications, and eliminates the attendant health services needed to treat those complications.

Clinical Pathway at Point of This Intervention

T2DM typically occurs in middle age or later, although incidence in a younger population has been growing as a result of the obesity epidemic. Initial treatment includes dietary modification, exercise, and self-monitoring of blood glucose. First-line drug therapies include biguanides,

sulfonylureas, alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, and dipeptidyl peptidase-4 inhibitors. Some patients require combination drug therapy of agents with different mechanisms of action for additive therapeutic effects and better glycemic control. Despite the availability of oral antidiabetes drugs, many patients do not achieve treatment goals and require additional therapy with an injected antidiabetes agent: subcutaneous insulin or a GLP-1 agonist.¹ The ITCA 650 implant would be used in place of injectable GLP-1 receptor agonists.

Figure 1. Overall high-impact potential: continuous subcutaneous delivery of exenatide by implantable pump (ITCA 650) for treatment of type 2 diabetes



Overall, experts commenting on this intervention agreed on the need for more effective T2DM treatments, citing patient adherence issues and the lack of efficacy of available treatments. Experts commented that this intervention has the potential to improve patient health by reducing the burden of frequent injections. Experts agreed on the potential for widespread acceptance by both clinicians and patients. Physicians would be attracted by the potential to reduce treatment variability through consistent drug delivery. Patients would likely accept this intervention because it may replace frequent injections with an annual procedure. Some experts thought that the initial cost of the device could be offset by long-term savings from reduced disease-related complications. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on ITCA 650 (subcutaneous exenatide).¹⁶⁻²¹ We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Most experts agreed that a large unmet need exists for new interventions that may help patients with T2DM better meet their treatment goals, given the large and growing population with diabetes. One health systems expert stated, “Adherence issues with oral drugs and insulin are significant.”²¹ However, another health systems expert thought that the availability of several other medications for T2DM lessened the unmet need that ITCA 650 purports to fulfill.¹⁶ Most experts thought that ITCA 650 has good potential to improve patient health and to fulfill the unmet need compared to available treatments. One clinical expert noted, “Lack of compliance to current type 2 diabetes drugs is a major contributor to poor glycemic control and microvascular complications of type 2 diabetes. ITCA 650 is likely to improve glycemic control because of its long duration of action. The preliminary data indicate a dose-dependent improvement in glycemic control in patients treated with ITCA 650.”¹⁸ However, two experts, with health systems and research backgrounds, were less confident that the intervention would improve patient health or fulfill an unmet need, and they wanted to see additional outcomes data from larger trials before fully embracing ITCA 650.^{16,19} One research expert noted, “For some patients, particularly those who have struggled with complying to treatment with self-injectable exenatide treatments,

ITCA 650 might improve health outcomes. However, in general, this treatment does nothing to change a patient's lifestyle approach."¹⁹

Acceptance and adoption: Overall, experts anticipated wide acceptance from physicians for improving the standardization of drug delivery. One clinical expert stated, "The current management of type 2 diabetes is largely ineffective. ITCA 650 is likely to gain wide acceptance among clinicians because the device is easy to implant, and the treatment is likely to improve glycemic control and reduce diabetes-related complications."¹⁸ One research expert stated, "As a more controlled treatment option for patients with T2DM, I foresee clinicians accepting ITCA 650. Offering this new form of exenatide therapy might also attract more patients and potentially even offer clinicians a new revenue stream, if the implantation procedure is charged separately."¹⁹ Experts thought that a large proportion of patients would choose this device for convenience and the possibility of improved outcomes through more consistent drug delivery, although some patients may continue to prefer regular injections to an implanted device. One clinical expert stated, "Most of the current drugs for type 2 diabetes have to be administered frequently, which leads to poor compliance. Most patients are likely to use ITCA because it offers a long-term possibility of improving glycemic control and preventing diabetes-related complications."¹⁸ Experts were somewhat divergent in estimating ITCA 650's cost impact. Most experts thought that the intervention would likely cost somewhat more than injectable exenatide or comparable drugs but holds some potential to reduce costs by lowering incidence of complications through more consistent drug delivery. One health systems expert opined, "I don't agree with potential to lower longer term costs. The out-of-sight, out of mind concept may play here, with patients not adhering to dietary/exercise regimens since they don't have to take/check insulin twice a day."¹⁶

Health care delivery infrastructure and patient management: Experts generally anticipated that introduction of ITCA 650 would create little disruption to either health care infrastructure or management of patients with T2DM. Clinicians would likely require minimal training in office-based device implantation, experts thought. Likewise, experts expected that patient followup would likely be similar because this patient population typically is monitored closely. One health systems expert suspected that the more consistent drug delivery might result in fewer diabetes-related emergencies necessitating acute treatment.¹⁶ This health systems expert also stated, "I fear that physicians will prescribe and walk away from the patient until the next insertion date, without providing the lifestyle management and encouragement necessary for type 2 diabetes mellitus."¹⁶

Health disparities: Generally, experts thought that ITCA would likely have a modest impact on health care disparities. However, they thought a disparity could emerge if the implantable drug dispenser is not covered by health insurers. If reimbursement were not widely available, then patients with lower socioeconomic status might be less likely to have access to ITCA 650, and these patients are often more widely affected by diabetes, most experts noted. One research expert noted, "As long as the medication were covered by payers, there should not be a large impact on health disparities. This device may be very important in reducing disparities in patient sub-populations who may not be able to self-inject exenatide, and for whom other oral medications are either not appropriate or insufficient to manage their blood glucose."¹⁷

Metabolic Surgery for Treatment of Type 2 Diabetes Mellitus Regardless of Patient BMI

Unmet need: Despite availability of new diabetes medications, behavioral and lifestyle therapies, glucose monitors, insulin pumps, and treatment protocols, two-thirds of patients with T2DM, especially those requiring insulin therapy, do not achieve adequate glycemic control. This increases their risk of secondary complications, including cardiovascular disease, nephropathy, neuropathy, and retinopathy.²²⁻²⁴ Observations that T2DM has resolved completely after various bariatric surgery modalities—independent of any resulting weight loss—in many morbidly obese patients who also had diabetes led to a study of the surgery’s impact on less obese patients with T2DM, and similar observations were made. This led to the reframing of bariatric surgery as metabolic surgery for treating refractory T2DM in patients who have been unable to achieve adequate glucose control with first- and second-line therapy, regardless of the patient’s body mass index (BMI). The approach focuses less on weight loss *per se* and more on addressing the metabolic abnormalities involved in diabetes.^{25,26}

Intervention: Metabolic surgery for T2DM has evolved as a surgical intervention intended to induce remission in patients who have been unable to achieve adequate blood glucose control with first- and second-line therapy. Although initially termed bariatric surgery and used to treat morbid obesity (BMI more than 35 kg/m² with at least one comorbidity [e.g., diabetes, hypertension] or with BMI of more than 40 kg/m²), this approach has been explored as a diabetes treatment regardless of patient BMI and independent of weight-loss goals.²⁶ Some clinical researchers believe that BMI-based criteria for bariatric surgery are not appropriate for determining eligibility in patients with T2DM because the primary goal of bariatric surgery (weight loss) is different from the primary goal of metabolic surgery (restoring metabolic dysfunction responsible for T2DM). Therefore, many obesity- or bariatric-surgery professional societies have added the term “metabolic” to their organization names, and many centers that use the surgery for weight reduction and separately for T2DM management include “metabolic” when referring to their surgery centers.^{27,28}

This distinction has contributed to a paradigm shift in surgery for T2DM from surgery directed at obesity alone to surgery directed at restoring metabolic imbalances, thereby loosening patient eligibility criteria from a focus purely on high BMI to a focus on treatment-refractory T2DM.²⁹ A consensus has been building that the metabolic improvements (e.g., normalization of glycemia) observed after metabolic surgery often precede weight loss in obese patients, and the improvements have occurred even in patients with BMIs lower than 35 kg/m² and lower even than 30 kg/m².²⁹ This suggests that a metabolic change, not weight loss, is likely responsible for the reduction or reversal of diabetes in these patients.²⁹⁻³¹

Metabolic surgeries for T2DM have been typically classified as purely restrictive, restrictive/malabsorptive, or purely malabsorptive; restrictive procedures limit food consumption, while malabsorptive procedures reduce food absorption.³² However, as the effects of various procedures become more evident, this terminology has become less useful for addressing the issues of metabolic surgery.²⁶ Researchers hypothesize that the effects of metabolic surgery extend beyond those of malabsorptive and restrictive strategies. Although the exact mechanisms of diabetes remission are unclear, researchers believe they are associated with multiple changes to patient anatomy and physiology, resulting in metabolic alterations.³³⁻³⁵

Most metabolic surgery procedures are done laparoscopically; however, laparoscopic surgery may be difficult in patients with intra-abdominal adhesions, or hernias. Therefore, metabolic

surgery may sometimes still be performed as an open procedure.^{26,32} Procedures most often considered to be metabolic surgeries are discussed here.

Purely restrictive metabolic surgical procedures. Laparoscopic adjustable gastric banding (LAGB) and vertical sleeve gastrectomy (VSG) reduce the stomach size to limit the rate and volume of food intake, decrease appetite, and increase feelings of satiety. In LAGB, a surgeon reversibly reduces stomach size by placing a band around the upper part of the stomach. In some studies, LAGB has been associated with T2DM resolution (or improvement) in as many as 80% of patients and excess weight loss of more than 30% (as much as 70%).^{36,37} VSG is an irreversible surgical procedure in which the surgeon excises a large portion of the stomach.^{38,39}

Restrictive/malabsorptive procedures. Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD) are performed with or without duodenal switch. As of 2011, RYGB was the most common type of metabolic surgery.⁴⁰ The procedure is primarily restrictive, although it has both restrictive and malabsorptive features. The surgeon partitions the stomach to form a small, 30 mL pouch where food will enter.³⁶ The surgeon then connects the distal small intestine to this gastric pouch. This connection creates the “Roux,” or alimentary limb of the Y-shaped construction. Next, the surgeon connects the duodenum portion of the upper small intestine to a distal section of the small intestine, thereby bypassing the duodenum and upper jejunum, creating the second limb of the “Y.”³⁶ In BPD, a surgeon performs a 60% distal gastric resection and creates a stapled closure of the duodenal stump to result in a stomach volume of about 300 mL.³⁶ With the duodenal switch, the surgeon performs a proximal gastric resection leaving the pylorus to control food drainage. Food and digestive nutrients mix in the remaining 50 cm of the bowel.^{36,40}

Purely malabsorptive procedures. These procedures are the jejunioileal bypass (JB), the duodenojejunal bypass (DB), and the investigational, device-based endoluminal sleeve (ES).^{29,33} In JB, a surgeon creates an ileal interposition linked to a diverted sleeve gastrectomy, thereby connecting the ileum, the lowest part of the small intestine, to the proximal intestine. This keeps digestive nutrients away from the bowel and limits small intestine length and absorptive surface area.³⁶ DB is a stomach-sparing bypass in which surgeons partially transect the duodenum 2 cm distal to the pylorus and perform duodenojejunal anastomosis to manipulate the intestine.^{40,41} The ES employs an impermeable gastrointestinal liner that is endoscopically inserted and anchored to the wall of the duodenum in a reversible procedure. The device blocks nutrient absorption from the stomach to the jejunum, thus reportedly mimicking the malabsorptive properties of RYGB surgery without permanently altering the patient anatomy.⁴²

Clinical trials: In March 2014, Muller-Stich and colleagues analyzed T2DM remission rates for 706 patients with T2DM and BMIs of less than 35 kg/m² enrolled in 5 randomized controlled trials and 6 observational clinical studies.⁴³ At followup from 12 to 36 months, metabolic surgery was associated with a higher T2DM remission rate (odds ratio [OR], 14.1; 95% confidence interval [CI]: 6.7 to 29.9; p<0.001), a higher rate of glycemic control (OR, 8.0; 95% CI, 4.2 to 15.2; p<0.001) and a lower HbA_{1c} level (mean difference [MD]: -1.4%; 95% CI, -1.9% to -0.9%; p<0.001) than medical treatment. After metabolic surgery, lower values were seen for BMI (MD, -5.5 kg/m²; 95% CI, -6.7 to -4.3 kg/m²; p<0.001), rate of arterial hypertension (OR, 0.25; 95% CI, 0.12 to 0.50; p<0.001), and dyslipidemia (OR, 0.21; 95% CI, 0.10 to 0.44; p<0.001).⁴³

In October 2014, Parikh and colleagues reported on remission rates and homeostatic model of insulin resistance (HOMA-IR) for 57 adults with T2DM and BMIs of 30–35 kg/m².⁴⁴ Investigators found that the surgery group had improved HOMA-IR (-4.6 vs. +1.6; p=0.0004) and higher diabetes remission (65% vs/ 0%; p<0.0001) than the medical weight management group at 6 months. Compared to the medical management group, the surgery group had lower HbA_{1c} (6.2 vs. 7.8; p=0.002), lower fasting glucose (99.5 vs. 157 mg/dL; p=0.0068), and fewer had T2DM medication requirements (20% vs. 88% of patients; p<0.0001) at 6 months. The surgery group also lost more

weight (7 vs. 1 kg/m² BMI decrease; $p < 0.0001$) than the medical management group. Higher baseline sRAGE (soluble form of receptor for advanced glycation end products) was associated with better weight loss outcomes ($r = -0.641$; $p = 0.046$). No deaths occurred. Surgery was very effective short-term in patients with T2DM and BMIs of 30–35 kg/m². Investigators concluded that baseline sRAGE may predict which patients might be most likely to benefit from metabolic surgery.⁴⁴

Manufacturer and regulatory status: Surgical procedures are not subject to FDA approval; however, the bands used in one of the procedures, gastric banding (e.g., Lap-Band, Realize), are subject to FDA regulation. Searches identified four manufacturers that distribute and market devices used for gastric band procedures.^{45–48} Commercially available technologies for metabolic surgery include the following:

- Heliogast HAGA, HAGE Gastric Band by Helioscopie (Vienne, France)⁴⁷
- Lap-Band Adjustable Gastric Band by Allergan, Inc. (Irvine, CA)⁴⁵
- Midband Adjustable Gastric Band by Médical Innovation Développement Co. (Dardilly, France)⁴⁸
- Realize adjustable gastric band by the Ethicon Endo-Surgery unit of Johnson & Johnson (New Brunswick, NJ)⁴⁶

Only one of the two approved devices has an indication that includes patients with BMIs of less than 35 kg/m², the Lap-Band.^{49,50} The device is indicated for use in weight reduction for patients with BMIs of 40 kg/m² or more or 30–40 kg/m² with one or more obesity-related comorbidity.^{49,51}

GI Dynamics, Inc. (Lexington, MA), is developing an ES device, the EndoBarrier, for treating T2DM and obesity. The device has received the CE mark, allowing marketing in Europe, and is being studied in U.S. pivotal trials.^{42,52}

Diffusion: Few reliable estimates of the diffusion of metabolic surgery are available because of the relative novelty of the procedure and varied technical approaches to performing it. A search of the U.S. National Clinical Trials Database (ClinicalTrials.gov) found almost 50 active trials (as of June 2015) evaluating some type of bariatric or metabolic surgery that mentions effect on diabetes or diabetes-related measurements as one of the outcomes. At least for the near future, modest diffusion of metabolic surgery would be expected without adequate insurance coverage for the procedure.

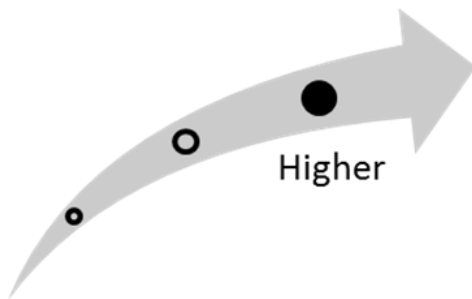
CMS has a national coverage determination titled “Surgery for Diabetes” that states, “Medicare currently covers bariatric surgery for persons with T2DM and BMI >35...and are non-covered for Medicare beneficiaries who have a BMI <35 and T2DM.”⁵³

Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield of Alabama, Blue Cross/Blue Shield of Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 9 outlining coverage for bariatric surgery for obesity, but these policies do not address metabolic surgery for treating T2DM. Furthermore, searches found no major payers with policies covering bariatric surgery for patients with BMIs of less than 35 kg/m². The policies on obesity surgery indicate that many of the benefit plans exclude coverage, but for the benefit plans that provide coverage, patients must have a BMI of more than 40 kg/m² or more than 35 kg/m² with a comorbidity.^{54–62} Two payers (Humana, Wellmark) indicate that patients who wish to undergo bariatric surgery may qualify for coverage if they receive a referral from their primary care physician. However, specific criteria for coverage are not currently provided by these payers.^{63,64}

Clinical Pathway at Point of This Intervention

Despite availability of new diabetes medications, behavioral and lifestyle therapies, glucose monitors, insulin pumps, and treatment protocols, two-thirds of patients with T2DM do not achieve adequate glycemic control. This increases their risk of secondary complications, including cardiovascular disease, nephropathy, neuropathy, and retinopathy.²²⁻²⁴ Clinical guidelines from the American Association of Clinical Endocrinologists, the Obesity Society, and the American Society for Metabolic & Bariatric Surgery state, “Patients with BMI of 30–34.9 kg/m² with diabetes or metabolic syndrome may also be offered a bariatric procedure although current evidence is limited by the number of subjects studied and lack of long-term data demonstrating net benefit.”²⁶ Thus, bariatric surgery intended to produce benefit beyond weight loss, otherwise defined as metabolic surgery, could conceivably be offered to treat T2DM and reduce cardiometabolic risk factors in patients whose disease is inadequately managed with more conservative medical management and lifestyle modification.

Figure 2. Overall high-impact potential: metabolic surgery for treatment of type 2 diabetes mellitus regardless of patient BMI



Most experts cited a large unmet need for improving diabetes management, with an increasing population with T2DM adding to the potential unmet need. Several experts noted metabolic surgery’s potential to put T2DM into remission rather than just manage the condition as supporting its large potential to improve patient health and fill a large unmet need. Most experts thought that metabolic surgery would represent a substantial disruption to how patients with T2DM are managed, compared to medical management and diet and lifestyle modification. Overall, experts expected that established bariatric surgery programs could add metabolic surgery to their programs with minimal disruption, unless insurance coverage becomes widely available, in which case substantial patient demand could develop. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.⁶⁵⁻⁷⁰ One clinical expert reported consulting relationships with manufacturers of obesity-related medical devices.⁶⁶ This potential conflict of interest is balanced by other expert reviewers who reported no potential conflicts of interest. We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Most experts cited a large unmet need for new therapeutic approaches to treat T2DM, given the growth of the T2DM population and the health risks and costs associated with complications from poorly managed disease. One research expert stated, “With close to 10% of the population affected by the disease and two-thirds of them not achieving adequate glycemic control, there exists an important gap to address.”⁶⁹ One clinical expert noted,

“There are millions of patients who may fit into the category of type 2 diabetes with BMI under 35. Metabolic surgery would provide an opportunity for improvement in many cardiovascular risk factors along with weight loss with fewer medications.”⁶⁷ However, one research expert saw little unmet need for metabolic surgery to fill, stating, “Despite the overwhelming number of patients with T2DM, there is really little to no need for an invasive intervention when a variety of other treatment options exist AND the disease is completely resolvable through diet and lifestyle changes.”⁶⁸ Most experts cited metabolic surgery’s overall potential to improve health outcomes and fill the unmet need.^{65-67,69,70} One research expert noted “pretty clear evidence that surgery improves diabetes, or even resolves it.”⁷⁰ One clinical expert stated, “There is a large potential to improve health outcomes with metabolic surgery. Unfortunately, at present we only have surrogate outcomes. Standard bariatric surgery has suggested fewer cardiovascular events and possibly fewer cancers in observational studies. Long term outcomes are needed with metabolic surgery vs. best medical therapy.”⁶⁷ Another clinical expert stated, “Metabolic surgery has the potential to put diabetes into remission. Pharmacotherapy can only manage the condition.”⁶⁶ One research expert cautioned, “While the data suggest that metabolic surgery may help control T2DM, the long term side effects of such intervention need to be considered as well as patient compliance with any required lifestyle changes.”⁶⁹ Another research expert generally disagreed, stating, “I still firmly believe that there are much better/favorable options for addressing T2DM, such as diet and lifestyle changes. One would think that a patient who is willing to modify his/her lifestyle after metabolic surgery (to cope with post-procedural effect), would be more than willing to pull their ‘all’ into this approach in an effort to avoid needing surgery in the first place.”⁶⁸

Acceptance and adoption: Experts were divided on acceptance by physicians and patients. Generally, most experts believed that acceptance by both groups could increase in the future if clinical data show long-term safety and efficacy and if coverage becomes available. Most experts did not anticipate metabolic surgery would be a first-choice treatment for most physicians or their patients. One clinical expert stated, “There is great potential here. However, patients, providers, and payors would need to be educated more effectively about that potential.... At present, many individuals with BMIs between 35 and 45 do not believe they are candidates for bariatric surgery. Many believe the procedures are reserved for those who weigh 600 lbs. Thus, lowering the BMI cutoff would not have a dramatic impact on patient volume for some time.”⁶⁶ This clinical expert added, “Endocrinologists will fight this to the death, as it would threaten their livelihood. Individuals who are anti-bariatric surgery currently would be opposed as well.”⁶⁶ Another clinical expert stated, “I think initially most clinicians would be hesitant to refer patients who are relatively healthy with BMI under 35 to surgery. If outcomes are shown to be better than a best medical approach and surgery is safe (as it is at present for bariatric surgery), acceptance should increase.”⁶⁷ This clinical expert expected a similar situation with patients: “While some patients would welcome this surgery as an alternative to a medical approach, I believe that many would avoid it initially. Over time, acceptance would increase, especially if the surgery and program is covered by insurance and could be done as an outpatient or with minimal hospital stay.”⁶⁷ One research expert stated, “I expect that for eligible patients, clinicians would be willing to prescribe this procedure. It could increase the number of patients receiving this type of surgery, which could increase revenues for the performing clinician. In addition, since it has been shown to be effective, it would provide clinicians the power to resolve their patients disease rather than asking them to make the changes necessary to do so themselves.”⁶⁸

Health care delivery infrastructure and patient management: Overall, experts expected metabolic surgery to have a modest impact on established bariatric surgery programs in the short term because the experienced staff and surgical facilities are already in place. However, most experts thought metabolic surgery could represent a substantially greater disruption to health care

infrastructure if the procedure were widely reimbursed by insurance plans and if patient demand increased, given the large population with T2DM. One research expert stated, “If all patients with diabetes had surgery, this would have a HUGE impact on the healthcare system, due to the multidisciplinary nature of surgery.”⁷⁰ Another research expert stated, “Performing surgery for metabolic disease would be a departure from how healthcare is currently delivered to these patients. Nevertheless, these types of surgeries are already being performed in patients who are obese or overweight with comorbidities. Therefore, for facilities already offering bariatric surgery, adoption of metabolic surgery is not likely to cause a large disruption. These centers would however, have to accommodate a potential increase in patient volume and educate staff on T2DM.”⁶⁸ A clinical expert stated, “If metabolic surgery for BMI under 35 were available and approved by insurance, there could be a significant influx of patients seeking this surgery. The clinics that prepare patients for bariatric surgery might need to hire extra staff including surgeons, behavioral providers, dietitians, and other medical providers.”⁶⁷ Another clinical expert stated, “If the recommended BMI criteria were to decrease, and payors would agree to cover those procedures, then volumes would increase and more professionals would have to enter the field. However, these scenarios would take years to play out.”⁶⁶ Several experts noted that metabolic surgery would be a substantial change from how most patients with T2DM are managed.^{65,68-70} One research expert stated, “Patients with T2DM have not conventionally been treated via inpatient, invasive, and in some cases irreversible, procedures such as...metabolic surgery. Therefore, an increase in the number of patients with T2DM seeking metabolic surgery would likely cause a substantial change in how patients with the disease are currently managed.”⁶⁸ A health systems expert noted, “As there is a long-term follow-up care needed for these types of surgery, there will be a disruption to how the care is carried out. These patients have to be on vitamins supplements, etc., for the rest of their lives as not as much nutrients are absorbed.”⁶⁵ However, two clinical experts anticipated small change to how most patients are managed because they expected that few patients would opt for metabolic surgery if given a choice, at least for the near future.^{66,67}

Health disparities: Experts offered mixed opinion on whether metabolic surgery could affect disparities. On one hand, several experts thought metabolic surgery could offer a substantial improvement in diabetes control and possible remission in less-affluent patients who are more affected by diabetes.^{66-68,70} One clinical expert stated, “The use of bariatric/metabolic surgery to treat obesity/T2DM is a huge health disparities issue. While minority groups are most commonly affected, they are far less likely to receive surgical treatment. In addition, those individuals from lower socioeconomic groups face environmental and economic challenges that make lifestyle modification and pharmacotherapy treatments less effective. Surgical intervention may represent their best chance to effectively treat obesity and T2DM.”⁶⁶ On the other hand, limited coverage from health plans has potential to increase disparities by restricting access to metabolic surgery to many patients who would likely benefit from it.^{65,67-70} One research expert stated, “Diabetes is overrepresented in poorer people. If they have less access to treatment, then disparities will increase.”⁷⁰ A clinical expert noted, “The potential to affect health disparities would depend on insurance coverage for metabolic surgery if it becomes a standard of care. If not covered by most insurances, those who could afford to pay for the surgery out of pocket would have an advantage leading to a difference in access.”⁶⁷

Threshold-Suspend/Low-glucose-Suspend Insulin Delivery System (MiniMed 530G with Enlite) for Managing Hypoglycemia in Patients with Type 1 Diabetes Mellitus

Unmet need: Fluctuating glucose levels make diabetes management and control difficult, often requiring adjustments to insulin dosage in patients with diabetes who require insulin.⁷¹ Researchers estimate that two-thirds of patients with diabetes do not achieve adequate glycemic control using traditional glucose meters and continuous glucose monitors (CGMs) to guide insulin treatment. This increases the risk of secondary complications, including cardiovascular disease, retinopathy, nephropathy, and neuropathy.²²⁻²⁴ Therefore, a medical need exists for systems that improve insulin delivery methods and glycemic control.⁷²

Intervention: The MiniMed 530G with Enlite[®] sensor is an external insulin pump used in combination with a continuous glucose monitoring sensor that can stop insulin delivery when glucose reaches a prespecified low level.⁷³ The system is the first insulin pump available in the United States to incorporate a low-glucose suspend (LGS) algorithm feature; the LGS algorithm automatically stops insulin delivery for up to 2 hours when sensor glucose values reach a preset level and when the patient does not respond to the threshold-suspend alarm.⁷⁴ The pump automatically resumes insulin delivery after the temporary suspension. Users who respond to the alarm can decide to resume basal insulin delivery or allow the pump to continue delivery suspension for up to 2 hours. The system also alerts users when the sensor detects the approach of potentially dangerous high glucose levels.⁷⁵ It is especially intended for use in patients who experience hypoglycemia without being aware of it.

The MiniMed 530G has been described as the first step toward development of a fully automated artificial pancreas device system. However, the system is not a closed-loop automatic pancreas because it does not automatically increase insulin infusion when hyperglycemia develops.⁷³

The MiniMed 530G consists of the following components that can be used in combination or individually:^{76,77}

- An insulin pump capable delivering insulin and storing 90 days of pump history and glucose sensor data
- Enlite sensors for continuous glucose monitoring, and Enlite Serter to facilitate sensor insertion
- MiniLink Real-Time transmitter that, when connected to a sensor, automatically initializes the sensor and periodically sends glucose data to the pump using a radio signal
- Contour NextLink glucose meter (Bayer Diabetes Care, Tarrytown, NY) that transmits fingerstick blood glucose results wirelessly to the insulin pump
- Bolus Wizard, which suggests a bolus amount to users based on their personal settings, blood glucose readings, carbohydrate entry, and active insulin levels
- CareLink[®] Pro, CareLink Personal therapy management software that uses information transmitted from insulin pumps, glucose meters, and CGMs to generate reports that can be used to identify trends and track daily activities (e.g., carbohydrates consumed, meal times, insulin delivery, glucose readings) in reports for clinicians and for patients

Users insert the glucose sensor through the skin in the abdomen to measure glucose values in the interstitial tissue. These values are transmitted to and displayed on the insulin pump.⁷⁸ The insulin pump delivers a small preset basal dose of rapid-acting insulin to the patient through an infusion set (a flexible delivery cannula with a small needle on the end) inserted under the skin in

the abdomen. Users must change the infusion site every two to three days. Also, users must perform a minimum of four fingerstick blood glucose tests per day using a glucose meter and manually administer individualized bolus doses of rapid-acting insulin via the pump to cover food intake and correct for high glucose levels.⁷⁸ The system requires a prescription

The manufacturer reports that its Enlite sensor can be worn for 6 days, is 69% smaller than the company's previous-generation sensor, and offers a 31% improvement in overall accuracy compared with the previous model. According to the company, "the new Enlite Serter provides a simpler sensor insertion process with a hidden-introducer needle."⁷⁴

The MiniMed 530G system uses the same calibration algorithm and threshold suspend software used in Medtronic's Veo™ insulin pump, which was developed earlier and is sold in Europe.⁷⁹ Like the MiniMed 530G system, the Veo insulin pump's LGS feature was designed to reduce the severity and duration of hypoglycemia. Patients may use the pump with or without CGM sensors, and CGM-augmented Veo pump users may turn the LGS feature on or off.⁸⁰

Clinical trials: In May 2015, Agrawal and colleagues reported a retrospective review of hypoglycemia incidence in 20,973 patients who used the MiniMed 530G insulin pump with the threshold-suspend feature either enabled or disabled.⁸¹ Investigators observed that patients enabled the threshold-suspend feature on 82% of patient-days reviewed. Sensor glucose values of 50 mg/dL or lower occurred 69% less often on patient-days when the threshold-suspend feature was activated than on patient-days when the feature was deactivated (0.64% vs. 2.09%, respectively; $p < 0.001$). When threshold-suspend was activated, the hypoglycemia reduction was more pronounced during nighttime than during daytime hours. Sensor glucose data from patients who used the threshold-suspend feature continuously showed a 62% reduction in sensor glucose values of 50 mg/dL or lower ($p < 0.001$), and a 5.6% reduction in sensor glucose values of 300 mg/dL or higher compared with data from nonusers ($p < 0.001$). The median sensor glucose value at the start of 2-hour insulin delivery suspensions was 60 mg/dL (interquartile range [IQR], 57–66). Median sensor glucose value immediately after 2-hour insulin delivery suspensions was 87 mg/dL (IQR, 63–123); 4 hours after insulin delivery suspension, median sensor glucose value was 164 mg/dL (IQR, 117–220).⁸¹

Manufacturer and regulatory status: Medtronic, plc (Dublin, Ireland) manufactures and distributes the MiniMed 530G with Enlite System in the United States.⁷⁶ In November 2012, FDA published guidelines, "The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Artificial Pancreas Device Systems," to inform the sponsors of IDE studies of artificial pancreas device systems on how to support a PMA for "single patient use in the home environment."⁸² In August 2013, FDA finalized the guidance and added it to resources about artificial pancreas research and development on its Web site.⁸³

In September 2013, FDA approved the MiniMed 530G with Enlite system.⁷⁶ The indication is "for use by people with diabetes ages 16 and older, requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin."⁷⁴

According to Medtronic's PMA submission for the MiniMed 530G, "A similar insulin pump system containing the threshold suspend tool received a CE mark under the name, Paradigm Real Time Veo System, and was commercialized in the European Economic Community in May 2010."⁷⁹ The summary of safety and effectiveness data for the MiniMed 530G states the following:⁷⁹

The effectiveness of the Threshold Suspend tool in correctly suspending insulin delivery at the set threshold was examined using the Sof-Sensor and the Medtronic Veo insulin pump. Though this system is not identical to the 530G system, this data can be extrapolated to support the safety and effectiveness of the 530G system for the following reasons. The software for the Threshold Suspend tool is the same for the Veo pump and the 530G System. Though the Medtronic Sof-Sensor and the

Enlite sensor are not identical, they operate using similar principles and fundamental scientific technology.

The MiniMed 530G System is the first to be approved under FDA's new product classification, "OZO: Artificial Pancreas Device System, Threshold Suspend." A threshold-suspend system is intended "to help reduce the severity or reverse a dangerous drop in blood glucose level by temporarily suspending insulin delivery when the glucose level falls to or approaches a low glucose threshold."⁸⁴ Additional FDA categories of artificial pancreas device systems include the following:⁸⁴

- Control-to-range systems that "reduce the likelihood of a hypoglycemic event or a hyperglycemic event by adjusting insulin dosing only if a person's glucose level approaches the low or high thresholds."
- Control-to-target fully automated systems that "set target glucose levels and try to achieve these levels at all times."

In accordance with FDA approval, Medtronic must conduct a longitudinal, multicenter postapproval study of the threshold-suspend feature with a sensor-augmented insulin pump in patients 16 years of age or older with insulin-requiring diabetes. The study goal is demonstrating that home use of the threshold-suspend feature is not associated with glycemic deterioration over 1 year.^{76,85} Medtronic will conduct the study at 50 investigational centers across the United States, enrolling up to 1,200 patients. Efficacy endpoints are overall mean change in HbA_{1c} level from baseline to 12-month followup and mean change in HbA_{1c} from baseline to end of study for each individual HbA_{1c} cohort (i.e., <7%, 7% to 9%, >9%).⁷⁶ Safety endpoints include serious adverse events, unanticipated device-related adverse events, incidence of severe hypoglycemia and severe hyperglycemia, and incidence of diabetic ketoacidosis.⁷⁶

Diffusion: An estimated 300,000 to 400,000 patients with type 1 diabetes mellitus (T1DM) in the United States currently use insulin pumps. Diffusion of the Medtronic MiniMed 530G with Enlite is occurring at an estimated 2,000 diabetes centers with multidisciplinary teams, which have the level of expertise and comprehensive training required to use and monitor device function.^{86,87} The most appropriate patients for the technology are considered to be those with T1DM who frequently experience hypoglycemia, are highly motivated to achieve control, and are able to use an insulin pump.^{88,89} Diffusion of the Medtronic MiniMed 530G began in late 2013. According to November 2014 correspondence, the manufacturer estimates that more than 53,000 MiniMed devices have been sold in the United States and more than 170,000 worldwide.⁹⁰

For a patient not currently using a Medtronic pump or CGM, the estimated cost to obtain the MiniMed 530G System and use it for a year would be \$14,550, which includes about \$4,500 for the Enlite Sensors.⁹¹⁻⁹³ Medtronic introduced a program to aid adoption called the Path2System Program.⁹⁴ This enables patients who already have an "existing, in-warranty Paradigm® Revel™ Insulin Pump and Continuous Glucose Monitoring" to order MiniMed 530G with Enlite Sensors for \$399 plus the varying cost of the Enlite starter kit. The Path2System includes the MiniMed 530G insulin pump; Enlite training packet; MiniLink transmitter, charger, and test plug; and Enlite Starter Kit. For patients currently using a Medtronic CGM, the estimated cost to obtain the MiniMed 530G System and use it for a year would be about \$7,975. Medtronic states that patients should expect a wait of 90 days after applying for the program because of high demand.⁹⁴ The retail price for MiniMed 530G was \$7,350 for those ineligible for the Path2System Program; insured patients reportedly typically pay \$500 to \$1,200 out of pocket, depending on their insurance copayments.⁹⁵ The company advises that patients' out-of-pocket costs for CGM vary according to their health plan coverage.⁹⁴

The U.S. Centers for Medicare & Medicaid Services (CMS) does not have a coverage policy for use of threshold-suspend insulin delivery systems. Therefore, coverage is left to the discretion of local Medicare carriers. CMS includes continuous subcutaneous insulin infusion by pump in its National Coverage Determination for infusion pumps.⁹⁶

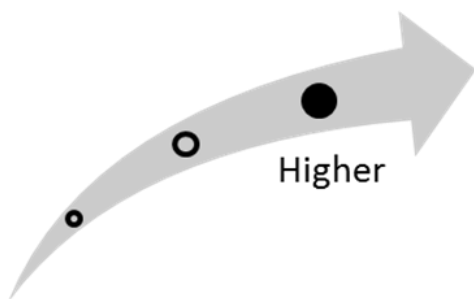
We searched 11 private, representative third-party payers to identify whether they have policies that mention the MiniMed 530G device. We found five policies indicating that the following payers provide coverage: Aetna,⁹⁷ Blue Cross Blue Shield (BCBS) of Alabama,⁹⁸ CIGNA,⁹⁹ Humana,¹⁰⁰ and Medica.¹⁰¹ These payers typically provide coverage when certain eligibility criteria are met, including the labeled indication criteria. Regence has a policy that states, “Use of an artificial pancreas device system is considered investigational. This policy is not intended to address insulin pumps which include a low glucose or low threshold suspend feature which may be considered medically necessary.”¹⁰² United HealthCare has a policy that states, “Devices classified by the U.S. Food and Drug Administration (FDA) as an artificial pancreas are unproven and not medically necessary.”¹⁰³

Clinical Pathway at Point of This Intervention

Upon receiving a diagnosis of diabetes, patients undergo medical evaluation to classify the disease type, detect any complications, review glycemic control challenges, and establish a treatment plan (depending on diabetes type and other medical factors). Part of this plan is establishing target HbA_{1c} goals. HbA_{1c} is a measure of the average amount of glucose in a patient’s blood over a 2–3 months, based on a single blood draw.²

Patients with T1DM require insulin therapy. For T2DM, one or more self-administered oral antidiabetes agents taken alone or in combination are generally tried as first-line therapy. Some patients with T2DM also need insulin therapy.² Clinicians encourage patients to achieve an HbA_{1c} level of about 7% or slightly lower, depending on the patient. This value has been shown to reduce some secondary complications associated with T1DM and T2DM. Patients and their diabetes care teams work to adjust insulin dosages using feedback from a blood glucose monitor.¹⁰⁴ The MiniMed 530G would be used similarly to other external insulin infusion pumps to replace the need for frequent insulin injections.

Figure 3. Overall high-impact potential: threshold-suspend/low-glucose-suspend insulin delivery system (MiniMed 530G with Enlite) for managing hypoglycemia in patients with type 1 diabetes mellitus



Overall, experts commenting on this intervention opined that it has the potential to improve health outcomes by improving disease management and reducing hypoglycemic episodes. Experts generally agreed on the potential for widespread clinician and patient acceptance. However, some experts cited cost, insurance coverage, and device training to be potential barriers to acceptance. Most experts agreed that this intervention is not likely to affect health disparities. However, one expert noted that the device has not been evaluated for use in pediatric patients with diabetes, a

group that could potentially benefit greatly from it. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on the MiniMed 530G with Enlite.¹⁰⁵⁻¹¹⁰ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: All experts noted the significant need for interventions that help improve continuous control of blood glucose levels in patients with diabetes who require exogenous insulin. One clinical expert stated, “Most diabetic patients on insulin therapy, possibly two-thirds or higher, do not achieve adequate glycemic control using glucometers and continuous glucose monitors. High glucose levels predispose to several complications, including cardiovascular disease, retinopathy, nephropathy, and neuropathy. Moreover, hypoglycemic episodes have been associated with higher cardiovascular events and mortality.”¹⁰⁶

Experts generally commented that this intervention has the potential to improve patient health outcomes by reducing hypoglycemic episodes. One research expert stated, “While ultimately more research is needed, the current technology has the potential to improve patient health by lowering the severity of hypoglycemic events and helping to stabilize blood glucose levels. However, the true potential to patient health lies in the future advancements of artificial pancreas device systems when hyperglycemic events can also be addressed.”¹¹⁰ A clinical expert noted, “The preliminary data show that the MiniMed 530G with Enlite system improves glycemic control and reduces hypoglycemic episodes. However, the long-term effects of this mode of insulin therapy on micro- and macro vascular complications of diabetes and mortality are unknown.”¹⁰⁶

Most experts thought the MiniMed 530G has good potential to fill the unmet need for improved diabetes management tools. One research expert noted, “Even as an incremental step towards a fully automated artificial pancreas device system, the MiniMed 530G with Enlite has the potential to fulfill the unmet need of providing technology to diabetic patients that will allow them to better control and manage their condition, specifically minimizing the effects of hypoglycemic events.”¹¹⁰ A clinical expert added, “The MiniMed 530G with Enlite system has a large potential to improve insulin treatment and glycemic control in type 1 diabetes patients or others requiring insulin therapy. The typical treatment of diabetes with multiple injections or insulin pumps, and frequent glucose testing using a glucometer is unsatisfactory. The MiniMed 530G with Enlite system is technically superior, improves glucose levels, and avoids hypoglycemia.”¹⁰⁶ However, one research and one health systems expert predicted a lower potential to fill the unmet need.^{108,109} The health systems expert stated, “The insulin pump with low-glucose suspend is a step toward a more life-like replacement of a human pancreas. While the technology itself is quite promising, it appears that adoption in the near future may be slow because of difficulty in achieving medically necessary criteria for insurance reimbursement, and the combination of low insurance reimbursement/high out-of-pocket expenses.”¹⁰⁸

Acceptance and adoption: All experts expected that both patients and physicians would widely accept this intervention because of the benefits of increased glycemic control. Some experts noted that the possible barriers to acceptance might be reluctance from clinicians to learn about a new insulin delivery system and teach it to patients, as well as some patients’ resistance to learning how to operate a new insulin pump. One health systems expert noted, “Some clinicians may resist learning about the new insulin delivery system. However, I think reducing the number of hypoglycemic events for their patients would outweigh this drawback.”¹⁰⁸ Likewise, the health

systems expert stated, “Patients may also resist learning how to use the new pumps. However, the prospect of reducing or eliminating hypoglycemic events” would be appealing.¹⁰⁸

Health care delivery infrastructure and patient management: Most experts anticipated little disruption to health care delivery infrastructure from use of the MiniMed 530G, given the experience with insulin infusion pump technology in general at many diabetes treatment programs. However, one health systems expert expected a larger disruption, stating, “Clinical staff will need to be trained on how to teach patients to use these new pumps, as well as troubleshoot equipment malfunctions and emergent events. Additional time and resources would need to be allocated in order to deliver the training to the patient as well as provide in home or telephone support. Training the patient on how to use the pump may need to happen over the course of days or weeks with followup.”¹⁰⁸ Similarly, most experts thought the MiniMed 530G would cause little disruption in the way that most patients, especially patients already using conventional insulin infusion pumps, would be managed. One research expert opined, “For outpatient clinics dedicated to diabetes management, the disruption is likely small as they are familiar with the specialized care of diabetes. However, there may be moderate disruption for [staff in] healthcare settings who are less familiar with, but must manage, the care of diabetic patients (e.g., inpatient stays, surgeries). Procedures, supplies, alarms, etc., may need to be addressed.”¹¹⁰

Health disparities: Most experts predicted that the technology would be unlikely to reduce any existing health care disparities. One clinical expert noted, “Most health disparities in diabetes affect patients with type 2 diabetes who are African-American, Native-American, or Hispanic. The MiniMed 530G with Enlite system will benefit patients with type 1 diabetes or other diseases requiring continuous glucose monitoring and insulin therapy.”¹⁰⁶ However, some experts suggested that the high cost and complexity of the technology could increase disparities for patients without adequate insurance coverage, if coverage is available.^{105,108,109} One health systems expert noted, “This technology has a high initial cost as well as high yearly consumable costs. Potential reimbursement from Medicare and Medicaid as well as third party payers appears low and would only be available after other diabetes mellitus treatment protocols had been proven to be ineffective. This treatment appears cost prohibitive for those without insurance. Individuals who do qualify for insurance but are of low socioeconomic status, homeless or migratory may not be able to maintain a relationship with a provider in order to meet criteria for insurance reimbursement.”¹⁰⁸ One research expert thought that technology might create a disparity in pediatric populations, stating, “Until there are studies to indicate the safety and effectiveness of the technology for patients 2 to 15 years old, a significant sector of the T1DM patient population that could benefit from a stage 1 artificial pancreas device system will not have access to the technology.”¹¹⁰

Ultra-Rapid-Acting Inhaled Insulin (Technosphere Insulin Inhalation System With Afrezza) for Treating Diabetes That Requires Insulin

Unmet need: Despite available insulin formulations, pumps, and oral antidiabetic medications, optimal glycemic control remains a challenge for many patients with diabetes who require insulin therapy.¹¹¹ Patients who do not achieve adequate glycemic control have an increased risk of secondary complications (i.e., cardiovascular disease, retinopathy, nephropathy, neuropathy).^{112,113} Difficulties with adherence to available insulin delivery methods and self-monitoring are two of the factors affecting adequate management.^{111,114} Therefore, a need exists for improved insulin delivery methods to aid adherence and improve glycemic control.

Intervention: The Technosphere[®] insulin inhalation system with Afrezza[®] powdered insulin is a noninjectable form of insulin therapy intended to improve glycemic control in adult patients with T1DM or T2DM.¹¹⁵⁻¹¹⁷ Afrezza is intended for prandial (mealtime) insulin therapy and is intended to reach peak insulin levels in about 12–15 minutes in contrast to the 45–90 minutes for injected rapid-acting insulin and 90–150 minutes for injected regular human insulin.¹¹⁸ Because of this rapid peak, Afrezza insulin is considered to be an ultra-rapid-acting prandial insulin.^{119,120} Afrezza is a combination drug-and-device product that consists of metered doses of human insulin powder in single-use cartridges and a “whistle-sized,” disposable inhaler to deliver the insulin powder. The inhaler can be used for up to 15 days if kept clean and dry.^{117,118} Afrezza insulin is administered using the manufacturer’s Technosphere technology, a dry-powder delivery platform that reportedly mimics intra-arterial administration. The intervention consists of insulin that is encapsulated in microspheres of fumaryl diketopiperazine (a proprietary excipient) and polysorbate 80 (a common emulsifier used in food and cosmetics).^{116,121,122} Upon inhalation, the patient’s breath powers the inhaler to aerosolize the powder so that it reaches the lungs and dissolves quickly. This allows insulin to be absorbed into pulmonary arterial circulation, to achieve rapid systemic delivery.^{116,118,119,121} The manufacturer asserts that because Afrezza’s effect lasts about 3 hours, hyperinsulinemia occurs less often, thus lowering hypoglycemia risks and hyperinsulinemia-related weight gain.^{118,120} The manufacturer also claims that Afrezza therapy results in lower fasting glucose than can be achieved using other available mealtime insulin therapy while providing comparable overall glucose control.¹²³ The manufacturer recommends a mealtime dosage adjustment to be made based on “the individual’s metabolic needs, blood glucose monitoring results and glycemic control goal.”¹²⁴ The single-use cartridges contain doses of 4 units (0.35 mg of insulin) or 8 units (0.7 mg of insulin). Patients self-administer the prescribed dose inhalation at the beginning of each meal and do not administer if a meal is skipped.^{118,125}

Clinical trials: In 2014, Afrezza’s manufacturer presented an overview of Afrezza clinical trials in its approved product labeling.¹¹⁸ Among 344 patients with T1DM, investigators compared mean reduction in HbA_{1c} between Afrezza plus basal insulin (n=174) and insulin aspart plus basal insulin (n=170). After 24 weeks, Afrezza plus basal insulin therapy “provided a mean reduction in HbA_{1c} that met the prespecified non-inferiority margin of 0.4%.” Combination therapy with Afrezza provided less HbA_{1c} reduction than combination therapy with insulin aspart, and the difference reached statistical significance. The company reported that more subjects in the insulin aspart group achieved the HbA_{1c} target of 7% or lower.¹¹⁸

Another trial compared Afrezza to placebo, both in combination with metformin only or two or more oral antidiabetic agents, in 479 patients with T2DM. After 24 weeks, investigators observed

that the Afrezza group had a statistically significant greater reduction in HbA_{1c} than the placebo group.¹¹⁸

The company also reported cumulative major adverse event data associated with Afrezza therapy in 1,026 patients with T1DM and 1,991 patients with T2DM. Patients exposed to Afrezza had received Afrezza therapy for at least 5 months and up to more than 1 year. Severe hypoglycemic events occurred in 5.1% (n=177) of the Afrezza group compared to 1.7% (n=176) of the placebo group among patients with T2DM. Afrezza therapy was associated with reduced pulmonary function that occurred during the first 3 months of therapy and persisted over 2 years. Trials lasted up to 2 years and excluded patients with chronic lung disease. Patients treated with Afrezza had a 40 mL (95% CI, -80 to -1) greater decline from baseline in forced expiratory volume in 1 second (FEV₁) than did patients treated with competing antidiabetes therapies. A 15% or larger decline in FEV₁ occurred in 6% of Afrezza-treated subjects compared with 3% of subjects who received competing therapies.¹¹⁸

Manufacturer and regulatory status: MannKind Corp. (Valencia, CA) in collaboration with Sanofi (Paris, France) developed Afrezza. In June 2014, FDA approved Afrezza for improving glycemic control in adults with diabetes mellitus.^{118,126} FDA classifies inhaled insulin delivery systems as combination products (i.e., drug-device) and has adopted Good Manufacturing Practice guidelines that require sterile production of inhalation products and devices used to deliver them.¹²⁷ In February 2015, the companies announced a commercial rollout of prescription Afrezza to retail pharmacies throughout the United States.¹¹⁷

FDA required a Risk Evaluation and Mitigation Strategy (REMS) for Afrezza approval, informing prescribers about potential associated risks including the serious risk of acute bronchospasm.¹²⁶ FDA advises that Afrezza should not be used in patients with chronic lung disease, such as asthma or chronic obstructive pulmonary disease, because of this risk. Thus, candidates should undergo pulmonary testing (spirometry [FEV₁]) to screen for respiratory conditions that would contraindicate use of Afrezza, as well as periodic followup spirometry to identify potential long-term respiratory problems.^{118,128} The most common adverse reactions associated with Afrezza in clinical trials were hypoglycemia, cough, and throat pain or irritation. As part of the approval, the companies agreed to several postmarketing requirements, including a study to assess safety and efficacy in pediatric patients and a trial to evaluate long-term cardiovascular and pulmonary risks. Also, two pharmacokinetic-pharmacodynamic studies will be initiated to characterize dose response and determine within-person variability.¹²⁶

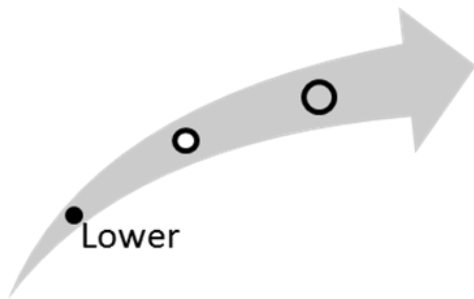
Diffusion: Although FDA approved Afrezza in June 2014, the manufacturer did not begin distributing the product to U.S. retail pharmacies until February 2015.¹¹⁷ Business media have reported slower-than-anticipated U.S. sales during Afrezza's first months on the market, due in part to some physicians' reluctance to prescribe the drug because patients must first undergo lung function tests to evaluate their suitability to use inhaled insulin.^{129,130} MannKind and Sanofi are reportedly planning direct-to-consumer multimedia marketing campaigns to persuade patients to request Afrezza from physicians as a strategy for increasing sales.¹³⁰ According to a U.S.-based, online aggregator of prescription-drug prices, GoodRx, as of June 2015, Afrezza's retail price ranged from about \$230 for a 90-cartridge kit at the 4-unit dose level to about \$310 for a kit containing 30 cartridges of 4 units each and 60 cartridges of 8 units each.¹³¹

Clinical Pathway at Point of This Intervention

T2DM typically occurs in middle age or later, although incidence in a younger population has been growing as a result of the obesity epidemic. Initial treatment includes dietary modification, exercise, and self-monitoring of blood glucose. First-line drug therapies include biguanides,

sulfonylureas, alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, and dipeptidyl peptidase-4 inhibitors. Some patients require combination drug therapy of agents with different mechanisms of action for additive therapeutic effects and better glycemic control. Despite the availability of oral antidiabetes drugs, many patients do not achieve treatment goals and require additional therapy with an injected antidiabetes agent: subcutaneous insulin or a GLP-1 agonist.¹ Afrezza is intended for prandial (mealtime) insulin therapy and is intended to reach peak insulin levels in about 12–15 minutes in contrast to the 45–90 minutes for injected rapid-acting insulin and 90–150 minutes for injected regular human insulin.¹¹⁸

Figure 4. Overall high-impact potential: ultra-rapid-acting inhaled insulin (Technosphere insulin inhalation system with Afrezza) for treating diabetes that requires insulin



Overall, experts anticipated good acceptance for inhaled insulin from physicians and patients. Some experts thought that although some clinical data suggest inhaled insulin might not always be as effective at glycemic control as injectable insulin, the convenience and improved comfort could improve outcomes by increasing adherence to insulin therapy. Experts noted that inhaled insulin represents only one component of a multifaceted treatment regimen for most patients with diabetes. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this technology.¹³²⁻¹³⁷ We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Overall, experts agreed on the need for new treatment options for patients with diabetes to improve compliance with recommended therapy and success at attaining treatment goals. One health systems expert noted, “Historically, patients do not like to self inject due to the pain, inconvenience, and social stigma of injecting a medication. Many insulin products require refrigeration, adding to the inconvenience, especially while traveling or eating out.”¹³⁵ Likewise, a clinical expert stated, “Diabetes is very prevalent in the United States. Many diabetic patients have poor control of their blood sugar level. Difficulty with adherence to multiple injections on a daily basis contributes to poor diabetes control. Therefore, any agent that decreases pain and inconvenience and other side effects of injectable insulin should improve adherence and thereby, diabetes control.”¹³⁶ Another clinical expert noted, “Inadequate glycemic control is a major problem in patients with type 1 or type 2 diabetes. Long-acting insulin injection improves baseline glucose; however, the control of meal related (prandial) glucose with injectable insulin is often suboptimal. Poorly controlled prandial glucose levels worsen HbA1C in the longterm, predisposing to vascular complications. Afrezza has potential to improve prandial glucose levels due to its rapid onset of action.”¹³² Although inhaled insulin represents only one component of the complete therapeutic regimen for many patients, most experts thought it has strong potential to improve

outcomes for that one care component: prandial insulin therapy. Several experts noted that although limited available data suggest that rapid-acting injectable prandial insulin might work better than inhaled insulin, inhaled insulin might improve outcomes by improving compliance because more patients might find it less painful and more convenient to take inhaled insulin.^{132,134-137} One clinical expert stated, “Afrezza decreases prandial glucose levels and lowers glycated hemoglobin, and thus would be expected to decrease the incidence of diseases associated with poorly controlled diabetes. The effect of Afrezza on HbA1c is less than for aspart insulin, a rapidly acting injectable insulin.”¹³² A research expert noted, “Availability of an insulin formulation that could more closely mimic pancreatic action and control rises in postprandial blood glucose is very important.”¹³⁴ One clinical expert who cited the intervention’s potential to improve patient health also pointed to the need for additional research to more clearly define inhaled insulin’s safety and efficacy. This clinical expert stated, “Observational data suggest potential side effects, such as a decrease in pulmonary function test parameters such as FEV1. While the FDA mandated risk evaluation and mitigation strategy (REMS) assessment is a step in the right direction, I do feel that a randomized controlled study to compare inhaled versus subcutaneous insulin is warranted.”¹³⁶

Acceptance and adoption: All experts anticipated good acceptance from physicians, albeit with some caveats, and patients, with likely patient acceptance somewhat higher than physician acceptance. One research expert noted, “Expect wide acceptance by physicians for patients with poorly controlled T2DM refractory to oral therapies who are averse to injecting insulin. Specialists caring for patients with T1DM are interested in inhaled insulin as an improved way to control rises in postmeal blood glucose.” One clinical expert noted, “Given the convenience factor, I do believe that Afrezza will be widely prescribed by physicians. However, if insurance companies do not cover the medication, then the medication is less likely to be widely adopted.”¹³⁶ Another clinical expert opined, “The device is small and easy to operate, and is likely to be accepted by clinicians compared to frequent injections. However, clinicians may be concerned about the pre-screening and monitoring requirements.”¹³² A research expert noted, “Clinicians would be concerned about imprecise dosing and patients making dosing mistakes with a new device.”¹³³ All experts thought that patients without pulmonary conditions and likely good candidates for inhaled insulin would prefer inhaled insulin to multiple injections for prandial insulin therapy. One research expert stated, “Patients would love the convenience.”¹³³

Health care delivery infrastructure and patient management: Experts generally expected that inhaled insulin would cause small disruptions to health care delivery infrastructure, although candidates would require preliminary respiratory screening to determine their suitability. One clinical expert noted, “There is minimal potential for disruption of healthcare delivery because the Afrezza treatment is self-administered. Nonetheless, patients have to be screened to determine their eligibility, trained to use the system properly, and monitored for adverse effects, e.g., hypoglycemia and pulmonary complications.”¹³² One research expert noted that inhalation is a new administration route for an existing drug, thereby minimizing any disruptions.¹³⁴ One health systems expert and a research expert opined that to the extent that glycemic control is improved, the future burden on health care infrastructure from treatment of secondary complications of diabetes might be reduced.^{135,137} Experts also anticipated a small change to the way that patients are currently managed. One clinical expert stated, “There will be a learning curve with the patients learning how to use their medication. This may require extra physician or nurse visits for patients to learn how to use their medication.”¹³⁶

Health disparities: Experts generally thought that inhaled insulin, which is easier to administer than injections, has potential to reduce health disparities in less-affluent populations, which are heavily affected by diabetes, provided that insurance coverage is available for this more costly intervention.¹³²⁻¹³⁷ However, most experts also thought that inhaled insulin could increase

disparities somewhat if it is not reimbursed by insurers and its cost is unattainable by many patients. One clinical expert noted, “However, given that there is a reasonable alternative (subcutaneous insulin) that is covered under most insurance plans, health outcomes overall should not decline in patients who cannot afford the inhaled insulin.”¹³⁶

Diabetic Macular Edema Intervention

Fluocinolone Acetonide Implant (Iluvien) for Treatment of Diabetic Macular Edema

Unmet need: The standard treatment for diabetic macular edema (DME) is laser photocoagulation to halt vision loss, but this treatment cannot reverse vision loss that has already occurred. Further, vision loss continues to progress in some patients despite treatment.¹³⁸⁻¹⁴⁰ Laser photocoagulation used in treatment may also be associated with a small increased risk of loss of peripheral, night, or color vision.¹³⁸

Recently, intravitreal injection has become a common treatment for DME. One such injected agent is ranibizumab, which FDA approved in 2012 for treating DME; it purportedly functions as an antiangiogenic agent. Additionally, because inflammation is thought to play a role in DME, off-label corticosteroid injections have been used by some retinal physicians to treat DME. Both antiangiogenic and corticosteroid treatments require ongoing treatment involving multiple intravitreal injections per year for effective treatment.^{141,142} Thus, interest exists in developing more convenient and safer intravitreal therapies for DME.

Intervention: Iluvien[®] is an intravitreal insert intended for sustained-release of the corticosteroid fluocinolone acetonide for treating DME.¹⁴³ The insert consists of 190 mcg of the drug in a tiny, cylindrical, polyimide tube designed to provide sustained drug release into the eye. The insert is delivered by intravitreal injection to the back of the eye with a 25-gauge needle, a needle size that purportedly allows natural physiologic sealing of the injection site. Iluvien is designed to have a therapeutic effect for up to 36 months through stable, long-term release of fluocinolone acetonide into the eye.^{143,144}

Clinical trials with Iluvien have demonstrated that patients with persistent DME responded well to Iluvien treatment despite poor responses to other treatments and that patients who had had DME for 3 years or longer responded better to treatment than those who had had DME for less than 3 years.¹⁴⁵ The exact mechanism for this improved visual acuity after treatment in patients with longer-duration DME is not known. Investigators hypothesize that chronic edema may exacerbate the inflammation that occurs in DME and that corticosteroids exert a therapeutic effect by modulating vascular permeability via several mechanisms including inflammatory cell inhibition, inflammatory cytokine downregulation, and stabilization of cell membranes and tight junctions.^{141,145}

Clinical trials: In a February 2013 analysis of two multinational trials in patients with DME previously treated with macular laser photocoagulation, authors reported that fluocinolone acetonide intravitreal implant 0.2 mcg/day was significantly more efficacious than sham injection in improving visual acuity. At 24 months after injection, 29% of recipients improved their best-corrected visual acuity (BCVA) letter score by 15 points or more compared with 16% in the sham injection group ($p=0.002$). The subgroup of patients whose DME duration was for 3 years or more achieved the greatest benefit, according to investigators. At 36 months, 34% of this subgroup increased their BCVA scores by 15 points or more compared with 13% of sham injection recipients ($p<0.001$). Fluocinolone acetonide intravitreal implant recipients also experienced generally more benefits than the control group on secondary endpoints. In patients who were phakic in the study eye at baseline, cataracts occurred in 82% of patients receiving the implant 0.2 mcg/day and 51% of sham injection recipients. Overall, 37% and 12% of patients in the fluocinolone acetonide intravitreal implant and sham injection groups developed elevated intraocular pressure (IOP), which was generally controlled with medication.¹⁴⁶

In June 2012, Campochiaro and colleagues reported results from 953 patients in the phase III (FAME[™]) trial, which evaluated over 36 months.¹⁴⁵ At 36-month followup, 28.7% of patients receiving a low dose and 27.8% of patients receiving a high dose of fluocinolone acetonide gained

15 points or more in letter score using the last observation carried forward method, compared with 18.9% in the sham group ($p=0.018$). Preplanned subgroup analysis demonstrated a doubling of benefit compared with sham injections in patients who reported a DME duration of 3 years or more at baseline. The percentage who gained 15 points or more in letter score at month 36 was 34.0% (low-dose group; $p<0.001$) or 28.8% (high-dose group; $p=0.002$) compared with 13.4% (sham group). An improvement 2 or more steps in the Early Treatment Diabetic Retinopathy Study (ETDRS) retinopathy scale occurred in 13.7% (low-dose group) and 10.1% (high-dose group) compared with 8.9% in the sham group. Almost all phakic patients in the medication-implant groups developed cataracts, but their visual benefit after cataract surgery was similar to that in pseudophakic patients. The incidence of incisional glaucoma surgery at 36 months was 4.8% in the low-dose group and 8.1% in the high-dose insert group.¹⁴⁵

Manufacturer and regulatory status: pSivida Corp. (Watertown, MA) developed the sustained-release, drug-delivery technology and licensed it to Alimera Sciences, Inc. (Alpharetta, GA).¹⁴⁷ In September 2014, FDA approved Iluvien for treating DME in patients “who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.”¹⁴⁸ Iluvien is also commercially available in the European Union for treating “DME considered insufficiently responsive to available therapies.”^{149,150}

Diffusion: The drug is likely to compete with laser photocoagulation and off-label corticosteroid injections for DME;^{141,142} these treatments cannot reverse vision loss that has already occurred, and vision loss continues to progress in some patients despite those treatments.¹³⁸⁻¹⁴⁰ Additional vision loss is also a risk associated with laser photocoagulation.¹³⁸ Fluocinolone acetonide could complement laser therapy and might be potentially more convenient and safer than corticosteroid therapy because it would not require ongoing intravitreal steroid injections; thus, patients might find it a more appealing option.

In the United States, the Iluvien implant costs about \$8,800, not including the costs of implantation and followup.¹⁵⁰ Associated implantation costs have not been widely reported since the manufacturer announced that the first products were shipped in late February 2015, following FDA approval in September 2014.¹⁴⁷ In the United Kingdom, the Iluvien implant costs an estimated £5,500, plus an additional £381 for the implantation procedure and another £240 for followup visits.^{151,152} At June 2015 exchange rates, estimated costs would be \$8,455 for the implant, \$586 for device implantation, and \$369 for patient followup.¹⁵³

The fluocinolone acetonide implant will probably compete with ranibizumab (Lucentis®), a vascular endothelial growth factor (VEGF) inhibitor approved for treating DME with monthly intravitreal injections.¹⁵⁴ According to GoodRx, ranibizumab cost an estimated \$2,000 per vial in June 2015 with the use of a coupon.¹⁵⁵

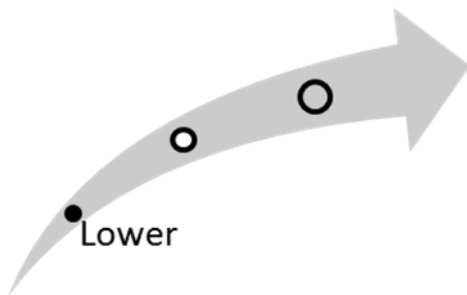
Additional DME treatment options under investigation include other corticosteroid medications and anti-VEGF agents. Ozurdex® (formerly Posurdex) is a biodegradable intravitreal implant that releases low doses of the corticosteroid dexamethasone over 4 months.^{156,157} The drug has been approved by FDA for treating DME, uveitis, and other ocular disorders.¹⁵⁸ Bevacizumab (Avastin®) and pegaptanib (Macugen®) are anti-VEGF (antiangiogenic) drugs typically used in cancer treatment and age-related macular degeneration; in clinical trials, researchers are testing the efficacy of small doses for treating DME.¹⁵⁹ In one recently completed phase IV study, researchers studied the efficacy of combining Ozurdex with bevacizumab for treating DME.¹⁶⁰ Bevacizumab is reportedly used widely for off-label treatment of ophthalmic conditions, including DME, as a significantly less-expensive alternative to ranibizumab.¹⁶¹⁻¹⁶⁴ However, some researchers report that intravitreal injections of bevacizumab are associated with a significantly higher rate of serious adverse events (because of the dose-preparation requirements for ophthalmic administration), which could pose an additional cost burden to treat. In one Canadian retrospective study, subjects who

received bevacizumab for ophthalmic indications were 12 times as likely to develop severe intraocular inflammation after each injection as were patients who received ranibizumab injections.¹⁶⁵

Clinical Pathway at Point of This Intervention

All patients with a diagnosis of diabetes mellitus are at risk of developing DME. A patient who presents with symptoms suggesting DME undergoes a history and physical examination pertaining to diabetes history, vision and eye-disease history, and other risk factors (i.e., older age, poor glucose control, pregnancy, hypertension, and increased lipid levels).¹⁶⁶ Using a high-magnification ophthalmoscope, the ophthalmologist can identify the retinal thickening that indicates macular edema. Yellow exudates and poor visual acuity may also be detected. DME treatment focuses on glycemic control, optimal blood pressure control, and macular focal/grid laser photocoagulation. Standard therapy has been laser photocoagulation and intravitreal injections of ranibizumab, off-label bevacizumab, or corticosteroids.¹⁶⁶ Use of Iluvien would replace frequent intravitreal injections for up to 3 years, according to the manufacturer.

Figure 5. Overall high-impact potential: fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema



The rising incidence of diabetes that raises the risk of vision problems including diabetic macular edema creates a large unmet need for more effective DME treatments, experts agreed. They opined that this implant has the potential to improve patient health outcomes and potentially access to care by increasing medication adherence and reducing the frequency of required clinic visits. However, several experts expressed concerns about potential adverse events, including a risk of cataracts and glaucoma. Clinician acceptance is likely to be moderated by the potential for adverse events, experts thought. Patients would be more likely to accept this intervention for its convenience, although they would also weigh risk of adverse events in consultation with their physicians. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, provided perspectives on the fluocinolone acetonide implant.¹⁶⁷⁻¹⁷³ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Most experts concluded that an unmet need exists, based on the rising incidence of diabetes, coupled with the varied effectiveness of and need for multiple applications of available therapies for DME. However, one health systems expert saw little unmet need due to the availability of competing treatments for DME.¹⁶⁷ Experts were split over the intervention's potential to improve patient health. Two research experts and a health systems expert

thought that Iluvien offers little added health benefit compared with repeated intravitreal steroid injections and that few available data compared Iluvien to alternate therapies.^{167,171,172} However, three clinical experts and a research expert believed that Iluvien's greatest benefit was its ability to provide long-term administration of steroids, which could improve treatment consistency and alleviate issues of treatment compliance or regular access to treatment associated with repeated steroid injections. One research expert noted, "Even if Iluvien is proven to be as effective as current drug treatment, its significance lies in its ability to be long-lasting (reportedly up to as long as 3 years). The longest implant prior to Iluvien was a dexamethasone implant that lasted about 4 months. Thus in terms of patient compliance, this is a significant advantage."¹⁶⁸ Another clinical expert stated, "There is definite, real potential to help in visual outcomes of patients with diabetic macular edema. We know steroids help improve vision, so longer-lasting steroids would help longer term as the preliminary data show. However the rate of development of glaucoma requiring surgery is not to be taken lightly.... Choice of who are the best candidates for the steroid implant may require some level of screening for glaucoma to avoid this complication."¹⁷⁰

Acceptance and adoption: Generally, experts anticipated moderate adoption of Iluvien by clinicians and patients, with patient acceptance trending somewhat higher. Experts thought that physicians and patients would weigh the convenience of one injection lasting 3 years versus the risk of cataracts and glaucoma. One health systems expert thought that the availability and amount of reimbursement for the Iluvien procedure compared with coverage of multiple steroid injections would greatly influence physician acceptance.¹⁶⁷ This expert also believes that costs would likely influence patient acceptance, stating, "Patients would most likely prefer this intervention as compared to the current intervention that requires much more frequent intraocular injections. I feel the deciding factor for most patients would be their out of pocket expenses."¹⁶⁷ One clinical expert noted, "Patients will like the idea of improved vision and reducing need for multiple injections. There is already an acceptance of intravitreal injections for retinal conditions, so I don't think that there will be any problem accepting this if doctor-recommended."¹⁷⁰ However, a research expert stated, "Initially, patients are likely to accept this treatment because of the single injection, but the risk of cataracts and glaucoma is high, which should temper their enthusiasm."¹⁶⁸

Experts generally thought that although Iluvien may be less costly than injections of anti-angiogenesis (anti-VEGF) drugs ranibizumab (Lucentis) or pegaptanib (Macugen), the risk of adverse events, such as cataracts or glaucoma, may reduce any potential savings. One research expert noted, "When compared with intra-vitreous injections of anti-VEGF drugs over a 2-3 year period, the projected cost of \$8,000 is significantly lower than ranibizumab (\$20,000-40,000/year) or Macugen [pegaptanib] (\$16,000-18,000/2 years). However, cost of treatment of adverse effects of cataract/glaucoma has not been taken into consideration, nor the loss of work days and disability due to these adverse effects."¹⁶⁸

Health care delivery infrastructure and patient management: Overall, experts thought that use of Iluvien would create few disruptions to health care infrastructure or current patient management procedures, at least in the short term. Implants would be injected in the same facilities where multiple steroid injections are administered now. The number of injections and office visits could be greatly reduced if the treatment lasts up to 3 years. One research expert stated, "Facilities performing photocoagulation procedures would probably do fewer of those procedures, which would be offset by an increase in implantation of Iluvien inserts."¹⁷³ However, experts also thought the risk of glaucoma and cataracts could increase health care use for the subgroup of patients in which they occur. One research expert noted, "Since Iluvien requires a single intra-vitreous injection (which is currently the mode of treatment with other drugs), no changes in physical resources should be anticipated. However if fewer visits are anticipated compared to current treatments, then number of staff might need to be reduced."¹⁶⁸ Another clinical expert stated, "The amount of care

that needs to be delivered has the potential to be higher due to complications with the risk of surgical intervention for glaucoma surgery, which includes more expenses for additional consultation for glaucoma diagnosis and decisions for surgery and possible costs to hospitals for indigent patients who may suffer from complications.”¹⁷⁰

Health disparities: Experts rated Iluvien’s potential effect on disparities from small to moderate to large. A health systems experts stated, “Due to its high cost and its minimal acceptance by insurers, I do not feel this intervention will aid in the decrease of any health disparities.”¹⁶⁷ One clinical expert noted, “Diabetic macular edema is more common in racial/ethnic groups with a higher prevalence of diabetes, i.e., Hispanic-, African-, Native Americans. Improved diabetic macular edema outcomes with Iluvien therapy is likely to decrease the incidence of blindness in these groups.”¹⁶⁹ Another clinical expert stated, “Because the complication rate for glaucoma surgical requirement is so high, this possible complication may not be well communicated or understood by certain groups of patients who have already been established to have higher risk for developing glaucoma (blacks/Hispanics) or poor followup in established glaucoma or glaucoma suspicion (low economic status and low literacy level).”¹⁷⁰ A research expert stated, “Iluvien is likely to have some effect on health disparities. The investigators report the cost of Iluvien to be \$8,000, which is significantly cheaper than Retisert. It is still a costly treatment and may be an option for patients with high economic status and/or those whose insurance coverage covers this treatment modality. The single injection will likely be an advantage in terms of patient compliance, fewer days missed from work when compared with multiple injections of other drugs. Thus, this may even out the disparity for low economic status/low literacy patients. However, the higher incidence of adverse effects (cataract and glaucoma) may have a counter effect.”¹⁶⁸

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